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(54) Title: A HAEMOSTATIC KIT, A METHOD OF PREPARING A HAEMOSTATIC AGENT AND A METHOD OF PROMOTING HAEMOSTATIS

(57) Abstract: A haemostatic kit to be used as a medical device provides for a containment unit and a haemostatic agent in said containment unit, said haemostatic agent occupying less than 90% of the volume of the containment unit. This allows for facile and consequently sterile preparation of, for instance, a gelatin paste for use in haemostatis when combined with saline, thrombin or another agent to assist in haemostatis.

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A HAEMOSTATIC KIT, A METHOD OF PREPARING A HAEMOSTATIC AGENT AND A METHOD OF PROMOTING HAEMOSTATIS.

FIELD OF THE INVENTION

5

A medical device comprising a powdered haemostatic agent in a containment unit suitable for adding a liquid to the agent and mixing the contents whilst still in the container allows for the sterile use of the haemostatic agent and greater ease of preparation. The haemostatic agent, such as collagen or a collagen-derived product such as gelatin, is present in a volume in the containment unit to allow for suitable mixing of any further agents, such as water, saline, or thrombin.

10

BACKGROUND OF THE INVENTION

The use of haemostatic agents provides for control of bleeding in surgical procedures.

15

Haemostatic agents supplement pressure, ligature and other conventional methods of controlling capillary, venous, and arterial bleeding.

The present investigators have commercialised a gelatin sponge as a haemostatic agent. A powdered agent some practical advantages in terms of surface area coverage and can be removed by irrigation and suction. Conventional powdered haemostatic agents are unpractical and risk either contamination of the sterile surgical field. The present invention addresses the risk of compromised sterility and contamination of the haemostatic agent by providing a kit which allows for the sterile and facile preparation of the powdered haemostatic agent.

20

WO 01/28603 relates to an injectable formulation for delivery of a composition comprising an osteogenic protein and a haemostatic gelatin foam paste as well as to a method of making a haemostatic gelatin foam paste suitable for injecting osteogenic protein, the method comprising hydration of Gelfoam® powder with glutamic acid buffer.

25

US 5,394,886 relates to a skin biopsy plug wherein the plug is a porous sponge made from gelatin material, which is implanted into a wound, swells, absorbs blood, and is completely absorbed in the patient. It relates to a combination of the punch (the blade for excising skin) and the plug. The plug used is the commercially available Gelfoam®.

30

US 5,645,849 claims a haemostatic patch comprising a biodegradable gelatin matrix, a haemostatic-promoting amount of thrombin and epsilon aminocaproic acid.

35

JP 62221357 discloses a skin ointment for promoting haemostatic effect comprising thermoplastic resin or rubber dissolved in solvent and contains dispersed gelatin powder. The product is an ointment comprising thermoplastic resin or rubber and a fine powder of
5 collagen, gelatin or chitosan.

FR 2679772 relates to particulate material to create an embolism comprising a polymer coated with a haemostatic or thrombogenic agent. The haemostatic agent may be a finely divided gelatin powder.
10

US 6,096,309 relates to a haemostatic composition comprising thrombin and a mixture of non-microfibrillar collagen and microfibrillar collagen in an aqueous medium wherein the microfibrillar collagen has an average fibril diameter of about 3-30 nm.

15 US 4,515,637 relates to both a method of forming a collagen-thrombin haemostatic composition and to a lysophilized collagen product, comprising collagen and thrombin.

US 6,045,570 relates to a gelatin powder for use as a haemostatic agent and to a biological sealant comprising a gelatin slurry which includes milled gelatin powder. The
20 slurry preferably comprises GelFoam® powder mixed with a diluent selected from saline and water. The slurry demonstrates superior flow characteristics in that it exhibits minimal dilatency and can be easily injected or introduced through catheter lumens, especially small lumens. The product therefore has very fluid characteristics.

25 GelFoam® is a commercially available product providing powdered gelatin for application to bleeding surfaces as a haemostatic agent. The powdered gelatin is provided in a full glass jar with a metal lid or in a sachet, each of which are to be opened and the contents of which, i.e. the gelatin, are to be poured into a sterile beaker or bowl. Contamination must be avoided during this process and a sterile technique must be employed when adding a
30 sterile saline solution. The problem of dispersion is avoided by initially compressing the powder with gloved fingers into the bottom of the beaker and then kneading it into the desired consistency. The powder is to be used as soon as the jar or sachet is opened and unused portions are discarded. This requires preparation of the haemostatic agent immediately prior to use. Contamination and sterility is not controlled by the product but
35 rather by the user and by the co-ordination of events following preparation of the agent.

Curacell® is a powdered haemostatic agent comprising oxidised cellulose, caboxycellulosum calcium which is applied as dry powder onto a bleeding area.

Avitene® is a microfibrillar collagen haemostat "flour" typically applied dry.

SUMMARY OF THE INVENTION

5 A first object of the invention relates to a medical device comprising:

i) a containment unit defining a first internal volume; said containment unit being comprised of a material substantially impermeable to fluid;

10 ii) a haemostatic agent of a second volume contained in said containment unit, said second volume being less than 90% of the first volume.

A further object of the invention relates to a haemostatic kit comprising

i) a containment unit said containment unit defining a first internal volume and

ii) a second volume of haemostatic agent

15 wherein the second volume relative to the first internal volume is such that the kit is suitable adding a third volume of liquid to said second volume and suitable for mixing said haemostatic agent within said containment unit.

Moreover, the invention relates to a process for preparing a haemostatic product

20 comprising the steps of:

i) providing a sterile containment unit having a first internal volume and at least one aperture for opening and comprising a second volume of haemostatic agent, said second volume being no more than 90% of the first volume;

ii) adding a third volume of liquid to said containment unit; and

25 iii) mixing the haemostatic agent and the liquid by shaking the containment unit.

A corresponding aspect of the invention relates to a method of promoting haemostasis comprising administering an effective amount of a putty-like paste comprising 20 to 33 % w/w of collagen to a patient in need of haemostasis, wherein the putty-like paste is

30 prepared according process defined supra.

An important object of the invention relates to the use of a containment unit defining a first internal volume and second volume of collagen or collagen-derived powder for the preparation of a haemostatic kit wherein the second volume is less than 90% of the first

35 volume.

DESCRIPTION OF THE INVENTION

The risk of compromised sterility and contamination of the haemostatic agent is addressed by the present investigators by providing a kit and medical device which allows for the
5 sterile and facile preparation of the powdered haemostatic agent. The present invention also allows for greater flexibility and ease of preparation of the agent. Surgeons state that the size of the bleeding area and the rate of the bleeding generally determine the consistency and amount of haemostatic agent. During a surgical procedure, these factors can suddenly and dramatically change. The present invention allows for a rapid, sterile and
10 facile preparation of the haemostatic agent. As stated, conventional products typically require the surgical staff to prepare the agent in advance using an additional mixing container.

A first aspect of the invention relates to a medical device comprising:

- 15 i) a containment unit defining a first internal volume; said containment unit being comprised of a material substantially impermeable to fluid; and
ii) a haemostatic agent of a second volume contained in said containment unit, said second volume being less than 90% of the first volume.

20 The term "second volume" is intended to mean a volume which is a subset within the first internal volume. That is to say that the second volume of the haemostatic agent is contained within the first internal volume; that the agent is contained within the containment unit.

25 The medical device is preferably such that the second volume is less than 85 %, of the first volume, preferably less than 80%, even more preferably less than 75% of the first volume, such as less than 70%, 65%, 60%, 55%, or 50% of the first volume, such as 70%, 65%, 60%, 55%, 50%, 40%, 30%, 20% and 10%.

30 In a typical embodiment, the haemostatic agent is in powder form. In a more typical embodiment, the haemostatic agent is collagen or collagen-derived powder. Preferably, said collagen or collagen-derived powder is gelatin. The gelatin may be derived from an animal or are synthetically made (recombinant). Suitably, the gelatin originates from porcine but may originate from other mammals. The powder is typically sterile

35

The powder is typically such that 95% of the powder is less than 1000 microns in size, preferably such that 90% of the second volume is less than approximately 700 μm . In a further preferred embodiment, 50% volume is less than approximately 350 μm .

The powder may be prepared from a gelatin sponge cut into pieces that fit into a mill and that will be bulk packaged into sterilization bags and placed in an oven (dry heat), for hardening for three hours. The gelatin plates raw material are typically manually fed into a rotor knife mill with a sieve for final grinding. The particle size is preferably such that not
5 more than 5% (w/w) is retained on a 1 mm mesh.

The containment unit typically comprises at least one opening and at least one closure-unit for closing the at least one opening. In an interesting embodiment, the closure-unit defines a second internal volume suitable for containing a liquid. The liquid may be present in the
10 closure-unit and this liquid can be released into the gelatin by a mechanical or physical action.

The closure-unit may itself comprise a rupturable membrane or the containment unit may comprise a rupturable membrane. This membrane may define a physical separation
15 between the second internal volume and the internal volume defined by the first internal volume and may allow for the combining of the liquid with the haemostatic agent by means of rupturing the membrane by any physical act such as by pressure or contact. The membrane may be ruptured (broken) by means of shaking the device. The rupturing of the membrane is preferably performed in such a manner so as to maintain the sterility of the
20 liquid and of the haemostatic agent.

Alternatively, the closure unit or containment unit may comprise a rupturable membrane which is perforated in order to inject the liquid, such as to maintain sterility of the agent. In this embodiment, the rupturable membrane divides the external environment from the
25 first and/or second internal volume. The rupturable membrane may be made of rubber or other suitable material and be perforated by injection of the liquid through a syringe or catheter.

The containment unit may comprise of grooves, protrusions or other physical distortions to
30 the otherwise parallel surfaces of the juxtaposed walls of the containment unit so as to ameliorate or facilitate the mixing of a liquid and the haemostatic agent.

In the embodiment wherein the haemostatic agent is collagen or collagen-derived powder, such as gelatin, it is suitably present in an amount from about 0.1 to 50 g, preferably from
35 about 0.2 to 20 g, even more preferably from about 0.4 to 10 g, most preferably from about 0.5 to 5 g, such as 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 g.

The containment unit is typically substantially rigid with at least one opening which may be closed with an appropriate closure-unit. The containment unit and closure unit are typically

comprised of a material independently selected from the group consisting of plastic, glass, metal or rigid or semi-rigid material. In a preferred embodiment, the material is selected from the group consisting of polypropylene, polyethylene, PVC and PET, more preferably polypropylene and polyethylene, most preferably polyethylene. Polyethylene is most
5 suitable for beta irradiation. The substantially rigid polyethylene or polypropylene container having a single opening may be sealed with a threaded, polyethylene or polypropylene closure. The closure-unit suitably comprises a dust-seal closure.

As stated, the containment unit defines a first internal volume; internal volume comprising
10 a haemostatic agent of a second volume, said second volume being less than 90% of the first volume. The volume difference is, at least in part, to allow for adequate addition of a third volume and mixing of the volumes. The dimension of the containment unit is suitably to facilitate the mixing. Typically, the dimension of the containment unit is also selected so as to allow for facile removal of the volumes onto the patient or other desired location.
15 Thus, the mouth of the containment unit must be suitably broad. Thus, commercially available wide-mouth or large-mouth containers are preferred.

In a particularly suitable embodiment, the haemostatic agent is present in a volume occupied by about one gram of powder, said second volume of haemostatic agent is
20 contained within a containment unit of about 50 to 100 cubic centimetres, such as about 60 to 90 cubic centimetres, such as about 70 to 80 cubic centimetres, typically about 75 cubic centimetres.

In the suitable embodiment wherein the haemostatic agent is present in a volume
25 occupied by about two grams of powder, said second volume of haemostatic agent is contained within a containment unit of about 75 to 200 cubic centimetres, such as about 80 to 180 cubic centimetres, such as about 90 to 170 cubic centimetres, such as about 100 to 160 cubic centimetres. Typically a second volume occupied by 2 g of powder is contained within a first internal volume of 100 to 200 cubic centimetres.

30 The medical device suitably further comprises iii) a third volume of a liquid. The liquid may blended with the haemostatic agent.

In a suitable embodiment, the liquid is in a unit physically separated from the haemostatic
35 agent. This physical separation may be in the form of a rigid internalised container in the containment unit or merely by means of a physical barrier which creates a non-porous divide between the agent and the liquid.

In an alternative embodiment, the liquid is in a second containment unit whose internal volume is physically separated from the first containment unit, such as to form a kit.

In a suitable embodiment, the liquid is thrombin. Thus, the medical may further comprise
5 thrombin. The thrombin may be present in the first containment unit or may be in a unit physically separated from the haemostatic agent or in a second containment unit containing said thrombin.

Thrombin, in a particularly suitable embodiment, may be added in an amount of 1-20 ml
10 per gram of powder, such as 5-15 ml, such as 7-12 ml.

The liquid may alternatively be selected from the group consisting of water and an aqueous solution such as saline. Suitably, the aqueous solution comprises an isotonicity-adjusting agent. The isotonicity adjusting agent may be sodium chloride, or known
15 equivalents to sodium chloride such as dextrose, various organic acids and their salts, inorganic salts such as boric acid, citric acid, tartaric acid and phosphoric acids.

The liquid may comprise thrombin and/or a bacteriostatic agent. Typically, the liquid is sterile
20

In a typical embodiment, the third volume of liquid is less than 35% of the second volume. The volume of liquid is preferably such that, when combined and mixed with the haemostatic agent, a doughy paste is formed. More suitably, the third volume is less than 33% of the second volume, such as less than 30%, less than 29%, less than 28%, less
25 than 27%, less than 26%, less than 25%, less than 24%, less than 23%, less than 22%, less than 21%, or less than 20%

The mixing of the liquid and the haemostatic agent is preferably performed by shaking the containment unit, most preferably the mixing is performed when the at least one opening
30 is separated from the external environment by the closure-unit. Shaking may involve swirling or agitation of any kind.

In a particularly interesting embodiment, the containment unit is surrounded with an outer wrap so that the containment unit is sterile. This will allow the user to remove the outer
35 packaging and transfer the containment unit into the sterile field. The user, in the sterile field, can then add the third volume of liquid, optionally by opening the containment unit to the external environment, adding by means of perforating the rupturable membrane of the closure-unit or containment unit, rupturing a seal which divides the closure unit from

the containment unit, as discussed supra, or pouring the liquid through the at least one opening of the containment unit.

- The medical device preferably further comprises an outer packaging defining a sterile barrier seal for enclosing said containment unit and maintaining sterility of the containment unit and its contents. The outer packaging may be peelable or removed from the outer surface of the containment unit. This containment unit is preferably enclosed in an outer packaging of a flexible, semi-rigid, or rigid plastic and/or metallic film providing a sterile barrier. The outer packaging typically consists of materials selected from the group consisting of Plastic/Aluminium foil/Plastic laminate where the plastic is selected from the group consisting of PET, PE, LLDPE, CPP, PA, PETP, METPET, Tyvek and optionally bonded with an adhesive (Polyurethane or other) or co-extruded. The outer packaging preferably forms a complete barrier to moisture.
- 15 The outer packaging may, in a particularly interesting embodiment, be able to endure radiation sterilisation at 3.5 Mrad (Beta) with a bioburden of less than 100 CFU/unit. A particularly interesting embodiment of the outer packaging included a pouch of laminated foil. The laminate may be PET, such as of approximately 12 microns in thickness.
- 20 The containment unit is preferably sterile. The containment-unit-facing side of the outer packaging and the containment unit are preferably sterile.

- The liquid is typically added so as to obtain a paste-like agent comprising 20-35 % wt/wt of w/w collagen powder, such as 25-33%, such as 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32% and 33%.

- A further object of the invention relates to a haemostatic kit comprising
- i) a containment unit said containment unit defining a first internal volume; and
 - ii) a second volume of haemostatic agent
- 30 wherein the second volume relative to the first internal volume is such that the kit is suitable to adding a third volume of liquid to said second volume and suitable for mixing said haemostatic agent said mixing proceeding within the containment unit.

- Preferably, the mixing occurs without present exposure to an environment external to that of the containment unit, typically without exposure to a non-sterile field.

The relative volume of the second volume of haemostatic agent relative to the first internal volume is less than in conventional products so as to be suitable for adding a third volume of liquid and for said liquid to be evenly and easily physically dispersed throughout the

second volume of haemostatic agent. Moreover, the mixing process, which accelerates the dispersion of the liquid evenly throughout the second volume of haemostatic agent, is facilitated and ameliorated by a low second volume-to-first volume ratio. Thus, in a particularly preferred embodiment, the second volume of haemostatic agent is less than 5 85% of the first internal volume, such as less than 80 % of the first volume, preferably less than 75%, even more preferably less than 70% of the first volume 65%, 60%, 55%, or 50% of the first volume.

The mixing process occurs within the containment unit and typically without present 10 exposure to an environment external to that of the containment unit. That is to say that a physical barrier, such as a closure-unit, typically separates the first internal volume, second volume of haemostatic agent and third volume of liquid from the external environment during the mixing process.

15 The third volume is an amount so as to obtain a putty-like paste from the haemostatic agent, preferably wherein the putty-like paste of the haemostatic agent comprises 20-35% wt/wt of w/w collagen powder, such as 25-33%, such as 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32% and 33%.

20 The containment unit is typically rigid, comprising at least one opening and one closure-unit and such that the mixing proceeds without loss of liquid and as described *supra*. The containment unit may be surrounded by a outer wrap/outer packaging se described *supra*.

A further aspect of the invention relates to a process for preparing a haemostatic product 25 comprising the steps of:

- i) providing a sterile containment unit having a first internal volume and at least one aperture for opening and comprising a second volume of haemostatic agent, said second volume being no more than 90% of the first volume;
- ii) adding a third volume of liquid to said containment unit; and
- 30 iii) mixing the haemostatic agent and the liquid by shaking the containment unit.

Typically, the mixing proceeds without present substantial exposure of said haemostatic agent and said liquid to an environment external to that the containment unit and without exposure to a non-sterile field. Preferably, the haemostatic agent is collagen or collagen- 35 derived powder, typically said collagen or collagen-derived powder comprises essentially of gelatin.

Preferably, in the process of the invention for preparing a haemostatic product, said haemostatic product is in the form of a putty-like paste comprising 20 to 99 % w/w of

collagen, preferably 20-80% collagen, such as 20-75% collagen, typically 20-70% collagen, such as 20-50%, 20-40%, 20-35%, 25-35%, such as 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, and 35% w/w.

- 5 The process typically involves the containment unit being rigid, and comprising at least one opening and one closure-unit and such that the mixing proceeds without loss of liquid.

The second volume is typically less than 85 % of the first volume, preferably less than 80%, even more preferably less than 75% of the first volume, such as 70%, 65%, 60%,

- 10 55%, or 50% of the first volume.

The process for preparing a haemostatic product may comprise the steps of:

- i) providing a containment unit having a first internal volume and at least one aperture for opening said aperture closed by a closure-unit and comprising a second volume of
15 haemostatic agent, said second volume being no more than 90% of the first volume;
ii) adding a third volume of liquid to said containment unit; and
iii) mixing the haemostatic agent and the liquid by shaking the containment unit.

- The sterile containment unit may further comprise an outer packaging defining a sterile
20 barrier seal for enclosing said containment unit, as described supra.

- A further aspect of the invention relates to a method of promoting haemostatis comprising administering an effective amount of a putty-like paste comprising 20-35 % wt/wt collagen powder, such as 25-33%, such as 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%
25 and 33% of collagen to a patient in need of haemostatis, wherein the putty-like paste is prepared according process as defined supra.

- The invention may be for use in any array of surgical procedures wherein bleeding or fluid control is preferred, such as in orthopedic procedures, such as laminectomy, total hip
30 replacement and hip revisions, knee surgery, spinal fusion; in cardiothoracic /cardiovascular procedures such as CABGs, valve replacements, aortic surgery, abdominal aortic aneurisms, carotid endarterectomy, and femoral-popliteal bypass, amongst others.

- A still further object of the invention is directed to the use of a containment unit defining a
35 first internal volume and a second volume of collagen or collagen-derived powder for the preparation of a haemostatic kit; wherein the second volume is less than 90% of the first volume such as 85% of the first internal volume, such as less than 80 % of the first volume, preferably less than 75%, even more preferably less than 70% of the first volume 65%, 60%, 55%, or 50% of the first volume.

The invention is further defined by the Examples.

EXAMPLES

5 Example 1

Product and Preparation

Clinical data (Example 2) was obtained on powder prepared from milling sheets of Surgifoam® sponge under a controlled process to produce a product meeting the following
10 specification:

The powder is a porcine gelatin based powder, off white in colour.

- 10% volume is less than approximately 90 μm ;
- 15 50% volume is less than approximately 350 μm ;
- 90% volume is less than approximately 700 μm ;
- as determined by laser diffraction.

The milled product is collected under slight negative pressure to avoid particulate emission
20 in the area and filled into a primary container, such as by using a hopper and scoop filling operation or by using pharmaceutical cGMP standard auger filling equipment.

The fill will be such that to be less than 75% of the volume of the primary container and checked by electronic scales so as to meet to desired pre-determined weight. A closure will
25 be applied.

The container will then be placed in a foil/film pouch which is sealed with a rotary heat sealer to form a moisture protection poach.

30 Alternatively, the batched containers will then be transferred to a blister packing room, such as a Multivac blister packing, where each container is packaged into a PETG/PE blister package. The blister packed product is loaded into irradiation boxes and subjected to pre-determined levels of e-beam irradiation.

Example 2**Clinical Data**

Clinical tests for effectiveness on general surgical procedures as well as cardiovascular and
5 orthopaedic surgical procedures were performed.

Study Design

An open label, randomised, controlled, multi-centre, unmasked study was conducted to
evaluate safety and effectiveness of two haemostatic agents. The study compared the
10 SURGIFOAM sponge from which the haemostatic powder is prepared to an absorbable
gelatin sponge currently legally marketed in the USA. The primary objective was to
examine the effectiveness as measured by haemostasis within 10 minutes of application.

Study Results

15 Two hundred and eighty one patients were enrolled in to the study and received study
treatment. The haemostasis data was collected immediately during the surgery and the
patients examined at 2 to 4 weeks and again at 6 to 8 weeks in order to obtain safety
data. The effectiveness data is summarised in Table 1.

Minutes	Device	General Surgery	Cadiovascular	Orthopaedic	Total
		%	%	%	%
3	Surgifoam	65.6	57.4	91.7	64.0
	Control	66.2	62.9	100	66.9
6	Surgifoam	98.4	80.9	100	90.1
	Control	95.4	91.9	100	94.2
10	Surgifoam	100	89.7	100	95.1
	Control	95.4	96.8	100	96.4

20 Table 1

Statistical analysis showed that SURGIFOAM and the control sponge were equivalent in the
ability to achieve haemostasis within 10 minutes.

Example 3**Evaluation of the Medical Device****Goal**

- 5 The purpose of this study was to measure both surgeons' and operating room nurses' perception of the device in terms of control of sterility and ease of preparation.

Method/Sample

- 10 12 interviews were conducted with operating room nurses who use haemostatic agents regularly.

Summary of Results

- 15 The surgeons and the nurses had complete acceptance and preference for a kit as defined by the present invention over conventional products.

Conventional Practice**20 Mixing of Conventional Products:**

- use of finger in a container separate than the agents container
- use of forceps or pickups or other surgical instruments in a container separate than the agents container

25 Disadvantages of Conventional Products:

- possible contamination in transferring product to separate mixing container
- bad smell
- non-sterile packaging
- powder is readily air-borne during opening and transfer process
- 30 • non-sterile container risks contamination of sterile field
- lengthy preparation due to requirement of additional bowl
- breathing in of air-borne powder
- wasted product in dispensing to mixing container

- 35 A medical device of the present invention was presented to the surgeons and the nurses of the test study. The response was such that the invention favourably addressed most or all of the disadvantaged of conventional products.

Example 4**Sealed pouches of laminated foil for containment unit**

- 5 The pouch must be able to endure radiation sterilisation at 3.5 Mrad (Beta) Bioburden less than 100 CFU/unit. With the Pouch A, suitable containment comprising 1 gram of powder allowed for the storage of the powder and the containment unit as sterile for extended periods of time (typically at least 4 years) without loss in the quality of the materials.

10	Material:	PET	12 microns
		Foil	8.75 microns
		Clear EZ Peel	50 microns
15	Size:	Width	6.5 inches
		Length	10 inches,

with a thumbnotch at the chevron end to allow for easy opening.

Provider Perfecseal

CLAIMS

1. A medical device comprising:
 - i) a containment unit defining a first internal volume; said containment unit being
5 comprised of a material substantially impermeable to fluid;
 - ii) a haemostatic agent of a second volume contained in said containment unit, said second volume being less than 90% of the first volume.
- 10 2. The medical device according to claim 1, wherein said second volume is less than 85 %, of the first volume, preferably less than 80%, even more preferably less than 75% of the first volume, such as 70%, 65%, 60%, 55% or 50% of the first volume.
3. The medical device according to any one of claims 1 to 2, wherein the haemostatic
15 agent is collagen or collagen-derived powder.
4. The medical device according to claim 3, wherein said collagen or collagen-derived powder is gelatin.
- 20 5. The medical device according to any one of the preceding claims further comprising
iii) a third volume of a liquid
6. The medical device according to claim 5, wherein the liquid is blended with the
haemostatic agent
25
7. The medical device according to claim 5, wherein the liquid is in a unit physically separated from the haemostatic agent
8. The medical device according to claim 5, wherein the liquid is in a second containment
30 unit whose internal volume is physically separated from the first containment unit.
9. The medical device according to any one of preceding claims further comprising thrombin or a containment unit containing thrombin.
- 35 10. The medical device according to claim 5, wherein the liquid is selected from the group consisting of water and an aqueous solution.

11. The medical device according to claim 10, wherein the aqueous solution comprises an isotonicity-adjusting agent.
12. The medical device according to claim 11, wherein the isotonicity adjusting agent is sodium chloride.
13. The medical device according to any one of claims 5 to 12, wherein the liquid comprises thrombin and/or a bacteriostatic agent.
- 10 14. The medical device according to claims 4 to 13, wherein the liquid is sterile.
- 15 15. The medical device according to any one of preceding claims, wherein said containment unit comprises at least one opening and at least one closure-unit for closing the at least one opening.
- 16 16. The medical device according to claim 15, wherein the closure-unit comprises a rupturable membrane.
- 17 17. The medical device according to any one of claims 15 to 16, wherein the closure-unit defines an internal volume suitable for containing a liquid.
- 18 18. The medical device according to claims 4 to 12, wherein the third volume of liquid is less than 20% of the second volume.
- 25 19. The medical device according to any one of preceding claims, wherein said collagen or collagen-derived powder is in an amount from about 0.1 to 50 g, preferably from about 0.2 to 20 g, even more preferably from about 0.4 to 10 g, most preferably from about 0.5 to 5 g, such as 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 g.
- 30 20. The medical device according to any one of preceding claims further comprising an outer packaging defining a sterile barrier seal for enclosing said containment unit.
21. The medical device according to any one of preceding claims, wherein the containment unit is sterile.
- 35 22. The medical device according to any one of claims 20 to 21 wherein the containment-unit-facing side of the outer packaging and the containment unit are sterile.

23. A haemostatic kit comprising
- i) a containment unit said containment unit defining a first internal volume and
 - ii) a second volume of haemostatic agent
- wherein the second volume relative to the first internal volume is such that the kit
- 5 is suitable adding a third volume of liquid to said second volume and suitable for mixing said haemostatic agent within said containment unit.
24. The haemostatic kit according to claim 23, wherein the third volume is an amount so as to obtain a putty-like paste from the haemostatic agent, wherein a putty-like paste of
- 10 the haemostatic agent comprises 20-33 % w/w of collagen powder.
25. A method according to claim 23, wherein said mixing proceeds without present exposure to an environment external to that of the containment unit.
- 15 26. The haemostatic kit according to any one of claims 23 to 24, wherein the containment unit is rigid, comprises at least one opening and one closure-unit and such that the mixing proceeds without loss of liquid.
27. The haemostatic kit according to any one of claims 23 to 26, wherein the second
- 20 volume of haemostatic agent is less than 90% of the first internal volume.
28. The haemostatic kit according to claim 27, wherein said second volume is less than 90 % of the first volume, preferably less than 85%, even more preferably less than 80% of the first volume, such as 75%, 70%, 65%, 60%, 55% or 50% of the first volume.
- 25 29. The haemostatic kit according to any one of claims 23 to 27, wherein the haemostatic agent is collagen or collagen-derived powder.
30. The haemostatic kit according to claim 29, wherein said collagen or collagen-derived
- 30 powder comprises essentially of gelatin.
31. The haemostatic kit according to claim 26, wherein the closure-unit comprises a rupturable membrane.
- 35 32. The haemostatic kit according to any one of claims 23 to 31 further comprising
- iii) said third volume of a liquid
33. The haemostatic kit according to claim 32, wherein the liquid is blended with the haemostatic agent

34. The haemostatic kit according to claim 32, wherein the liquid is in a unit physically separated from the haemostatic agent
- 5 35. The haemostatic kit according to claim 32, wherein the liquid is in a second containment unit whose internal volume is physically separated from the first containment unit.
36. The haemostatic kit according to any one of claims 23 to 35 further comprising
- 10 thrombin or a containment unit containing thrombin.
37. The haemostatic kit according to claim 32, wherein the liquid is selected from the group consisting of water and an aqueous solution.
- 15 38. The haemostatic kit according to claim 37, wherein the aqueous solution comprises an isotonicity-adjusting agent.
39. The haemostatic kit according to claim 38, wherein the isotonicity adjusting agent is sodium chloride.
- 20 40. The haemostatic kit according to any one of claims 23 to 39, wherein the liquid comprises thrombin and/or a bacteriostatic agent.
41. The haemostatic kit according to claims 23 to 40, wherein the liquid is sterile.
- 25 42. The haemostatic kit according to any one of preceding claims, wherein said containment unit comprises at least one opening and at least one closure-unit for closing the at least one opening.
- 30 43. The haemostatic kit according to claim 26, wherein the closure-unit defines an internal volume suitable for containing a liquid.
44. The haemostatic kit according to claims any one of claims 23 to 43 , wherein liquid is an amount less than 20% of the second volume.
- 35 45. The haemostatic kit according to any one of claims 23 to 44, wherein said haemostatic agent is in an amount from about 0.1 to 50 g, preferably from about 0.2 to 20 g, even more preferably from about 0.4 to 10 g, most preferably from about 0.5 to 5 g, such as 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 g.

46. The haemostatic kit according to any one of claims 23 to 45 further comprising an outer packaging defining a sterile barrier seal for enclosing said containment unit.
- 5 47. The haemostatic kit according to any one of claims 23 to 45, wherein the containment unit is sterile.
48. The haemostatic kit according to any one of claims 23 to 47, wherein the containment-unit-facing side of the outer packaging and the containment unit are sterile.
- 10 49. A process for preparing a haemostatic product comprising the steps of:
- i) providing a sterile containment unit having a first internal volume and at least one aperture for opening and comprising a second volume of haemostatic agent, said second volume being no more than 90% of the first volume;
 - 15 ii) adding a third volume of liquid to said containment unit; and
 - iii) mixing the haemostatic agent and the liquid by shaking the containment unit.
50. The process for preparing a haemostatic product according to claim 49, wherein the mixing proceeds without substantial exposure of said haemostatic agent and said liquid to
- 20 an environment external to that the containment unit.
51. The process for preparing a haemostatic product according to any one of claims 49 to 50, wherein the haemostatic agent is collagen or collagen-derived powder.
- 25 52. The process for preparing a haemostatic product according to claim 51, wherein said collagen or collagen-derived powder comprises essentially of gelatin.
53. The process for preparing a haemostatic product according to any one of claims 49 to 52, wherein said haemostatic product is in the form of a putty-like paste comprising
- 30 99 % w/w of collagen.
54. The process for preparing a haemostatic product according to any one of claims 49 to 53, wherein the containment unit is rigid, comprises at least one opening and one closure-unit and such that the mixing proceeds without loss of liquid.
- 35 55. The process for preparing a haemostatic product according to any one of claims 49 to 54, wherein said second volume is less than 85 % of the first volume, preferably less than 80%, even more preferably less than 75% of the first volume, such as 70%, 65% or 60% of the first volume.

56. The process for preparing a haemostatic product according to claim 49 comprising the steps of:

- i) providing a containment unit having a first internal volume and at least one aperture for
- 5 opening said aperture closed by a closure-unit and comprising a second volume of haemostatic agent, said second volume being no more than 90% of the first volume;
- ii) adding a third volume of liquid to said containment unit; and
- iii) mixing the haemostatic agent and the liquid by shaking the containment unit.

- 10 57. The process for preparing a haemostatic product according to claim 49 wherein the sterile containment unit is further comprises an outer packaging defining a sterile barrier seal for enclosing said containment unit.

- 15 58. The process according to claim 57, wherein the containment unit comprises a surface which makes at least partial contact with the outer packaging the containment-unit-contacting side is sterile.

59. A method of promoting haemostatis comprising administering an effective amount of a putty-like paste comprising 20 to 33 % w/w of collagen to a patient in need of
- 20 haemostatis, wherein the putty-like paste is prepared according process defined in to any one claims 49 to 58.

60. Use of a containment unit defining a first internal volume and second volume of collagen or collagen-derived powder for the preparation of a haemostatic kit wherein the
- 25 second volume is less than 90% of the first volume.

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MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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(54) Title: A HEMOSTATIC KIT, A METHOD OF PREPARING A HEMOSTATIC AGENT AND A METHOD OF PROMOTING HEMOSTASIS

(57) Abstract: A hemostatic kit to be used as a medical device provides for a containment unit and a hemostatic agent in said containment unit, said hemostatic agent occupying less than 90% of the volume of the containment unit. This allows for facile and consequently sterile preparation of, for instance, a gelatin paste for use in hemostasis when combined with saline, thrombin or another agent to assist in hemostasis.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 31955 A (BRAUN MEDICAL INC ;LIPOSOME CO INC (US)) 30 November 1995 (1995-11-30)	1,6-8, 14,15, 17,21, 23,25, 26, 32-35, 41-43, 49,50, 54,56
Y	page 3, line 3 -page 4, line 35	1,3,4, 9-16,19, 20, 22-24, 29-31, 36-41, 46,48, 49, 51-53, 57,58
	-/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *G* document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>page 6, line 20 -page 9, line 21 page 10, line 14 -page 11, line 34 page 13, line 7 -page 14, line 7 claims; figures</p> <p>---</p>	
Y	<p>US 6 045 570 A (LEMPERT TODD E ET AL) 4 April 2000 (2000-04-04) cited in the application</p> <p>column 7, line 21 -column 8, line 24 claims</p> <p>---</p>	<p>1, 3, 4, 9-14, 19, 24, 29, 30, 36-41, 51-53</p>
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 59
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 59 has not been searched in accordance with Art. 17(2)8a)(1), 17(2)(b) and Rule 39(1)(iv) PCT.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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(54) Title: A HEMOSTATIC KIT, A METHOD OF PREPARING A HEMOSTATIC AGENT AND A METHOD OF PROMOTING
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(57) Abstract: A hemostatic kit to be used as a medical device provides for a containment unit and a hemostatic agent in said
containment unit, said hemostatic agent occupying less than 90% of the volume of the containment unit. This allows for facile
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